

PATENT COOPERATION TREATY

27 SEP 2004

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

Schüssler, Andrea
HUBER & SCHÜSSLER
Truderinger Strasse 246
D-81825 München
ALLEMAGNE

HUBER & SCHÜSSLER
Patentanwälte

05. Aug. 2004

Frist:

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing

(day/month/year)

04.08.2004

Applicant's or agent's file reference
K 3142 Wd

IMPORTANT NOTIFICATION

International application No.
PCT/EP 03/03277

International filing date (day/month/year)
28.03.2003

Priority date (day/month/year)
17.04.2002

Applicant

DEUTSCHES KREBSFORSCHUNGSZENTRUM ... et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:



European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized Officer

Wallentin, M



Tel. +31 70 340-3991



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

27 SEP 2004

Applicant's or agent's file reference K 3142 Wd		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/EP 03/03277	International filing date (day/month/year) 28.03.2003	Priority date (day/month/year) 17.04.2002	
International Patent Classification (IPC) or both national classification and IPC C07K14/705			
Applicant DEUTSCHES KREBSFORSCHUNGSZENTRUM ... et al.			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 9 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 3 sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the opinion</p> <p>II <input type="checkbox"/> Priority</p> <p>III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p>IV <input type="checkbox"/> Lack of unity of invention</p> <p>V <input checked="" type="checkbox"/> Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI <input type="checkbox"/> Certain documents cited</p> <p>VII <input type="checkbox"/> Certain defects in the international application</p> <p>VIII <input type="checkbox"/> Certain observations on the international application</p>			
Date of submission of the demand 14.11.2003		Date of completion of this report 04.08.2004	
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016		Authorized Officer Schalich, J Telephone No. +31 70 340-3954 	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP 03/03277

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-29 as originally filed

Claims, Numbers

1-15 received on 13.07.2004 with letter of 13.07.2004

Drawings, Sheets

1/7-7/7 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☒ furnished subsequently to this Authority in written form.
☒ furnished subsequently to this Authority in computer readable form.
☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☒ the claims, Nos.: 16-23
☐ the drawings, sheets:

**INTERNATIONAL PRELIMINARY
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5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-15 (incomplete)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-15 (incomplete)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	10,11
	No: Claims	1-9,12-15
Inventive step (IS)	Yes: Claims	10,11
	No: Claims	1-9,12-15
Industrial applicability (IA)	Yes: Claims	1-9,12-15
	No: Claims	

2. Citations and explanations

**INTERNATIONAL PRELIMINARY
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see separate sheet

Re Item I

Basis of the report

The amendments filed with the letter dated 13.07.2004 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. The amendments concerned are the following:

"composition for diagnosis of a defect of the wnt/frz/lrp5,6 cascade"

According to the Applicant's letter, dated 13.07.2004, the basis for new claims 1-7 is found in old claims 1, 2 and 8 and the description (p 1-4). However, in said passages a basis is only found for "composition for diagnosis of aberrant expression of kremen 1 and 2".

Consequently, new claims 1-7 go beyond the disclosure of the international application as filed. According to Rule 70.2 (c) said claims have therefore been examined, as if said amendment had not been made, meaning, that new claims 1-7 refer to a "composition for diagnosis of aberrant expression of kremen 1 and 2".

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. ligands and modulators

Present **claims 1-15** relate to compounds defined by reference to a desired characteristic or property, namely to bind to or modulate the activity of Kremen 1 or 2. The claims cover all compounds having said characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the diseases and compounds by reference to a result to be achieved, but no technical features according to Rule 6.3. (b) PCT are given. A skilled person can not reduce to practice definitions as given in said claims, since there exist potentially limitless structural possibilities, comprising structures yet to be made, whereas it is not even possible to distinguish said claims over the state of art, since this would entail testing all known compounds/compositions for said activities (modulating or binding).

Consequently, during examination the terms ligand, activator/ agonist, inhibitor/ antagonist and pharmaceutical compositions will be understood as :
antibodies, antisense polynucleotides, specifically binding to said polynucleotide/
polypeptide, and dkk1 and 2

2. "supporting regenerative processes"

Present **claim 11** moreover relates to a condition defined exclusively in functional terms, namely to a process supporting regeneration. Since the description only provides support for bone tissue formation and the International Search Report was restricted thereto, during examination said term will be understood as "supporting bone tissue formation".

3. **Claims 10 and 11** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document/s/:

- D1: VAN ES JOHAN H ET AL: "You Wnt some, you lose some: Oncogenes in the Wnt signaling pathway." CURRENT OPINION IN GENETICS & DEVELOPMENT, vol. 13, no. 1, 20 February 2003 (2003-02-20), pages 28-33
- D2: BROWN SHERYL D ET AL: "Isolation and characterization of LRP6, a novel member of the low density lipoprotein receptor gene family." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 248, no. 3, 30 July 1998 (1998-07-30), pages 879-888
- D3: NAKAMURA T ET AL: "Molecular cloning and characterization of Kremen, a novel kringle-containing transmembrane protein" BIOCHIMICA ET BIOPHYSICA ACTA, AMSTERDAM, NL, vol. 1518, no. 1-2, 19 March 2001 (2001-03-19), pages 63-72
- D4: US 2001/036643 A1 (HOLLOWAY JAMES L) 1 November 2001 (2001-11-01)
- D5: EP-A-0 911 399 (SMITHKLINE BEECHAM CORP) 28 April 1999 (1999-04-28)
- D6: DATABASE EMBL [Online] 26 June 2001 (2001-06-26), XP002249432
retrieved from EBI Database accession no. AAB95341
- D7: DATABASE EMBL [Online] 6 November 2001 (2001-11-06), XP002249370
retrieved from EBI Database accession no. AAM93480
- D8: WO 02/066509 A (GENENTECH INC) 29 August 2002 (2002-08-29)
- D9: BAFICO A ET AL: "NOVEL MECHANISM OF WNT SIGNALLING INHIBITION

MEDIATED BY DIKKOPF-1 INTERACTION WITH LRP6/ARROW" NATURE
CELL BIOLOGY, MACMILLAN PUBLISHERS, GB, vol. 3, July 2001 (2001-07),
pages 683-686

D10: MAO BINGYU ET AL: "LDL-receptor-related protein 6 is a receptor for Dickkopf
proteins." NATURE (LONDON), vol. 411, no. 6835, 2001, pages 321-325

D11: WO 00/77239 A

D12: WO 01/34621 A

D13: WO 02/02603 A

1. Novelty and Inventive Step (Art. 33(2) and (3) PCT)

The present application does not meet the criteria of Article 33(1) PCT, because the
subject-matter of **claims 1-9 and 12-15** is not new in the sense of Article 33(2) PCT.

1.1. D11 discloses human TANGO 202, which is identical with human Kremen 1 (SEQ
ID 2 of the present application). D13 discloses a nucleic acid, coding for the human
protein modification and maintenance molecule 6 (PMMM-6), 100% identical with
Kremen 2 (SEQ. ID. 3). The other cited documents refer to nucleotide sequences,
which reveal an equal or higher degree of homology than the mouse sequences,
disclosed in present fig. 2 and 3, and therefore fall within the scope of present claims 1-
7. The claimed functions of the proteins, disclosed in D3-D7 and D11-D13, are
irrelevant for the binding of the claimed ligands.

- D4 (abstract and claims 1-3) discloses the gene and protein ztsg1, which is 94.3%
homologous to kremen 1. The compositions, it discloses (par 0137, 0257, par
221-226, abstract and claim 4), therefore fall under the scope of present claims 1-
7 and 12-15.
- D5 (claims 1 and 2) discloses the kringle-related gene and protein HTHBZ47,
which is 95.6% homologous to Kremen 1. Therefore also D5 (par 0039 and 0045-
0048, claim 3) renders present claims 1, 3-7 and 12-15 not novel.
- D11 discloses human TANGO 202, which is identical with human Kremen 1. The
compositions disclosed in D11 (p 4, last par and p97-102) therefore anticipate
present claims 1-7 and 12-15.
- D12 discloses a human kringle domain containing protein 1 (KDC1), which is
95,3% homologous to human Kremen 1. Present claims 1-7 and 12-15 are not
novel over the compositions disclosed on p 22 and p52 to 75.
- D6 (SEQ ID NO: 17621) discloses a polynucleotide encoding a polypeptide with
99,5% homology to Kremen 2 and primers hybridizing thereto, anticipating claim

1.

- D13 (p45, li 30 to p 46, li 19), disclosing the human protein modification and maintenance molecule 6 (PMMM-6), identical with Kremen 2 (SEQ. ID. 3), discloses compositions according to present claims 1-7 and 12-15.

Therefore **claims 1-7 and 12-15** are not novel.

1.2. Present claims 8 and 9 refer to methods of identification of binding partners and modulators of Kremen 1 and 2, which are however not novel over documents D5, D11 and D13

D5 (claim 6 a and b) discloses methods of identifying a binding partner of HTHBZ47, rendering present **claim 8** not novel, and D5 (claims 6 c-e) methods of identifying activators/ inhibitors of HTHBZ47, rendering present **claims 9** not novel.

Claims 8 and 9 are moreover not novel over D11 (p 136, par 4 to p 139, par 2 and p 122, par 2 to p 129, par 2) and D13 (p 47, li 23-27; p 53, li 21-28 and claims 19 and 22).

1.3. The subject-matter of **claims 10 and 11**, when restricted to the use of kremen 1,2 (genes and gene products), and antisense oligonucleotides and antibodies binding thereto, for inhibition of the wnt/frz/LRP5,6 cascade, seems to be novel and inventive, since no document, belonging to the state of the art, could assign the function of being a coinhibitor of the wnt/frz/LRP5,6 cascade to kremen 1 or 2.

2. Industrial Applicability (Art. 33(4) PCT)

Claims 1-8 and 12-15 are industrial applicable.

For the assessment of the present **claims 10 and 11** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

3. Support and disclosure (Art. 5 and 6 PCT)

Lack of technical support in the description for inhibition of wnt signal cascades in general by Kremen 1,2

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In **claim 10**, the Applicant discloses the use of kremen 1 or 2 as well as agonists, antagonists and ligands of said polypeptides for the preparation of a medical composition for inhibiting the wnt signal cascade. The description only provides support for inhibition of the wnt/frz/LRP5,6-cascade by kremen 1 or 2 in combination with dkk 1 or 2.

Document D2 (p28, co2, par 2 till p29, co 1, par 1) shows, that several wnt-signalling pathways exist, induced by several wnt-molecules in combination with different frz-receptors plus or minus diverse coreceptors, which activate independently several different transcription activators, leading to totally different gene expression patterns. The extension of the use of kremen 1 or 2 to inhibition of wnt signalling in general is thus also an unsupported generalisation. **Claims 10 and 11** will only comply with Art. 5 and 6 PCT, when said use is restricted to the inhibition of the wnt/frz/LRP5,6 signaltransduction cascade.

What is claimed is:

1. Use of

- (a) a nucleic acid molecule encoding human Kremen 1 and having the nucleotide sequence as depicted in Figure 1 or human Kremen 2 and having the nucleotide sequence as depicted in Figure 2,
- (b) a nucleic acid molecule which is capable of specifically hybridizing to the nucleotide sequence encoding Kremen 1 as depicted in Figure 1 and/or to the nucleotide sequence encoding Kremen 2 as depicted in Figure 2; or
- (c) at least one ligand which is capable of specifically binding to a Kremen 1 and/or Kremen 2 polypeptide.

for the preparation of a composition for diagnosis of a defect of the wnt/frz/LRP5,6 cascade.

2. The use of claim 1, wherein the ligand is an antibody.

3. The use of claim 1 or 2, wherein the nucleic acid molecule has a length of at least 10 nucleotides.

4. The use of any one of claims 1 to 3, wherein the nucleic acid molecule or ligand are detectably labeled.

5. The use of claim 4, wherein the label is selected from the group consisting of a radioisotope, a bioluminescent compound, a chemiluminescent compound, a fluorescent compound, a metal chelate, or an enzyme.

6. The use of any one of claims 1 to 5, wherein the nucleic acid molecule or ligand are bound to a solid support.

7. Use according to claims 1 to 6, wherein the target to which the nucleic acid molecule hybridizes is an mRNA.

8. A method for identifying a binding partner to a Kremen 1 and/or Kremen 2 polypeptide comprising:

- (a) contacting said polypeptide with a compound to be screened; and
- (b) determining whether the compound effects an activity of said polypeptide or whether binding of the compound to said polypeptide has occurred.

9. A method for identifying activators/agonists or inhibitors/antagonists of a Kremen 1 and/or Kremen 2 polypeptide comprising the steps of:

- (a) incubating a candidate compound with said polypeptide;
- (b) assaying a biological activity, and
- (c) determining if a biological activity of said polypeptide has been altered.

10. Use of a nucleotide molecule encoding a polypeptide having a biological activity of Kremen 1 and/or Kremen 2, a Kremen 1 and/or Kremen 2 polypeptide, an activator/agonist of a Kremen 1 and/or Kremen 2 polypeptide or binding partner of said polypeptide(s) for the preparation of a pharmaceutical composition for inhibiting the Wnt signal cascade.

11. Use according to claim 10 for supporting regenerative processes.

12. An activator/agonist or inhibitor/antagonist of a Kremen 1 and/or Kremen 2 polypeptide or binding partner of said polypeptide(s) obtainable by the method claim 8 or 9.

13. A pharmaceutical composition comprising a compound which is capable of modulating the expression of a nucleic acid

molecule (a) encoding human Kremen 1 and having the nucleotide sequence as depicted in Figure 1 or human Kremen 2 and having the nucleotide sequence as depicted in Figure 2 or (b) which is capable of specifically hybridizing to the nucleotide sequence encoding human Kremen 1 as depicted in Figure 1 and/or to the nucleotide sequence encoding human human Kremen 2 as depicted in Figure 2 or the activity of Kremen 1 and/or Kremen 2, and a pharmaceutically acceptable excipient, diluent or carrier.

14. The pharmaceutical composition of claim 13, wherein the compound stimulates expression of the gene encoding Kremen 1 and/or Kremen 2 or the activity of Kremen 1 and/or Kremen 2.

15. The pharmaceutical composition of claim 13 or 14, wherein the compound is a nucleotide molecule encoding a polypeptide having a biological activity of Kremen 1 and/or Kremen 2, a Kremen 1 and/or Kremen 2 polypeptide, an activator/agonist or inhibitor/antagonist of a Kremen 1 and/or Kremen 2 polypeptide or binding partner of said polypeptide(s) obtainable by the method of claim 8 or 9.